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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|------------------|
| 10/074,976 | 02/13/2002 | Robert J. Hariri | 011307 | 1042 |
| 20583 | 7590 | 09/23/2004 | EXAMINER | |
| JONES DAY 222 EAST 41ST ST NEW YORK, NY 10017 | | | | LI, QIAN JANICE |
| | | ART UNIT | | PAPER NUMBER |
| | | 1632 | | |

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|-----------------|-------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/074,976 | HARIRI, ROBERT J. | |
| | Examiner | Art Unit | |
| | Q. Janice Li | 1632 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 02 July 2004.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) 13-21 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-12,22 and 23 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 21 March 2002 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 5/15/02, 7/9/02.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) Notice of Informal Patent Application (PTO-152)
6) Other: _____.

DETAILED ACTION

The Examiner assigned to examine your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Q. Janice Li, at Group Art Unit 1632.

Election/Restrictions

Applicant's election of Group I, drawn to claims 1-12, 22, and 23, in the response filed 6/2/04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 13-21 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse.

Claims 1-12, 22, and 23 are under current examination.

Claim Objections

Claims 4-10 are objected to because of the following informalities: the word "including" should be deleted.

Claims 22 and 23 are objected to because "including" should be replaced with "wherein".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 22, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because claim 1 requires seeding ES cells in a tissue matrix, but since most ES cells would be differentiated as soon as they are seeded, it is unclear what cell *component* and *status* the "seeded tissue matrix" comprises, e.g. ES cells only or a specific type of differentiated cells. Claim 2, on the other hand, reads on seeding the collected residual cells in the perfusion liquid of the placenta, which would lead to a mixture of cells, rather than only ES cells, seeded in the tissue matrix. It is unclear what type of tissue matrix the claims are intended to make, and claiming, and thus the metes and bounds of the claims are unclear.

Claim 2 is vague and indefinite because the sequential timing of the claimed steps is unclear. Claim 2 recites that the steps of claim 1 *further* comprising perfusing a placenta. However, since the stem cells have been collected from a treated placenta in claim 1, it is unclear what does said perfusing the placenta have to do with preparing the tissue matrix, and thus the metes and bounds of the claims are uncertain.

Claim 4 recites the limitation "the placenta". There is insufficient antecedent basis for this limitation in the claim.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: identification of embryonic stem cells. Claim 1 requires collecting ES cells from a placenta, and Claim 3 requires separating ES cells from other residual cells and perfusion liquid. However, it is unclear how the ES cells are separated. Claim 6 further states that ES cells are separated by centrifugation; however, centrifugation does not appear to be able to separate ES cells from residual cells. Applicants are reminded that method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

Claims 22 and 23 are vague and indefinite because claims recite “before seeding said collected stem cells onto or into tissue matrix, stimulating said placenta with exogenous cells”. Since the stem cells have been collected from the placenta, it is unclear what does said stimulating the placenta have to do with preparing the tissue matrix. Further, it is unclear what type of exogenous cells are used and how to “stimulating”? Thus the metes and bounds of the claims are unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 22, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement*; Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The claims are drawn to a method of making a tissue matrix for implantation into a patient comprising seeding a tissue matrix with embryonic stem cells from a placenta, the tissue matrix made, and a method of using such for treatment. Here, the critical element for making and using the instantly claimed invention is the embryonic stem cells from a placenta. However, the specification has not set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the

invention to establish that the embryonic stem cells are indeed present in a mammalian placenta.

In view of the teachings of the specification, it defines embryonic stem cells (ES cells) as "derived from the inner cell mass of a blastocyst and pluripotent" (Specification, page 5, lines 24-26), which is consistent with the common knowledge concerning the source of ES cells. Apparently, a placenta is not the inner cell mass of a blastocyst, and has fully differentiated to a specified organ, and thus, cells obtained from a placenta are not art recognized ES cells even though it is known that they containing multipotent stem cells.

The specification goes on to teach that human placental stem cells are surprisingly embryonic-like, because certain cell markers such as SSEA3, SSEA4, OCT-4 and ABC-p have been identified in these cells (Specification, page 28, lines 13-20). However, this teaching appears to be prophetic because in the section entitled "isolation of placenta embryonic-like stem cells" (Specification, pages 43-44), applicants admitted, "no attempts were made to further characterized these adherent cells" and "when subcultured, the placenta-derived embryonic-like stem cells ... adhered within hours, assumed characteristic fibroblastoid shape, and formed a growth pattern identical to the reference bone marrow-derived MSC". In the result section that follows, the specification only discloses using CD-34 and CD38 markers, which are not ES cell markers. Assuming that applicants have reduced to practice that the placenta cells do contain cells having surface markers such as SSEA3, SSEA4, OCT-4, these markers alone cannot confirm the identity of ES cells. This is evidenced by the teaching of *Pera*

et al (J Cell Sci 2000;113:5-10), who listed the marker expression in mouse and primate ES cells including SSEAs, and Oct-4 in table 1, and stated, "IT MUST BE NOTED THAT NONE OF THESE SURFACE MARKERS IS COMPLETELY SPECIFIC AND ALL CAN BE DETECTED IN OTHER TISSUE TYPES. THE MARKERS ANALYSED THUS FAR IN THE PRIMATE OR HUMAN ES OR EG CELLS ARE ONLY IMMUNOCHEMICALLY DEFINED EPITOPE OR ENZYMATIC ACTIVITIES; THERE IS YET LITTLE INFORMATION ON GENE EXPRESSION IN HUMAN ES CELLS OR PRIMATE ES CELLS" (page 8). In the publication, *Pera et al* teach that SSEA3 and SSEA4 are present in human but not mouse ES cells, and further present in human embryonic carcinoma cells, and the presence of OCT-4 in human ES cells are questionable (table 1).

More importantly, the identity of ES cells has always been confirmed in the art by the functional testing, i.e. the ability of self-renew and differentiation (e.g. *Thomson et al*, Science 1998;282:1145-7). To this end, the specification is completely silent concerning the functional characteristics of the placenta ES cells, i.e. the ability to generate cells of identical properties (self-renew) and to give rise to differentiated cells types. Accordingly, the specification fails to disclose any evidence that the ES cells are indeed present in the mammalian placenta, either from the surface marker standpoint or from the capability of self-renewal and differentiation. The specification further fails to disclose the amount of ES cells that could be isolated, and the functional characteristics of the ES cells by either reduction to practice or describing the identifying characteristics of the placenta ES cells, which would show that applicant was in possession of the claimed invention. Therefore, it is concluded that the specification does not provide a written description of the claimed invention in such a way as to reasonably convey to

one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The courts have stated that the specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonable conclude the inventor had possession of the claimed invention see *In re Vas-Cath, Inc.* 935F2d. 1555, 1563, 19 USPQ2d 1111,1116

Claims 1-12, 22, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

These claims require the isolation and use of placenta ES cells, however, as indicated *supra* in the written description section, the specification fails to provide an adequate description for the purposed ES cells encompassed by the claims. Since the disclosure fails to describe the characteristics that identify the placenta ES cells or reduction to practice to show that such cells are indeed present, the skilled artisan cannot use the invention without first carrying out undue experimentation to determine whether such ES cells are indeed present in the placenta. Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claim 11 reads on a therapeutic product comprising a tissue matrix seeded with ES cells, and Claim 12 reads on a therapeutic method for using such product. However, it is well known in the art that the ES cells have not been used as therapeutic means because it is very difficult to obtain sufficient amount of human ES cells and differentiating the ES cells in a controlled manner to a desired cell type. This is evidenced by the teaching of *Donovan and Gearhart* (Nat 2001 Nov;414:92-97), who teach "SO FAR, THERE HAVE BEEN FEW DEMONSTRATIONS THAT DERIVATIVES OF STEM CELLS CAN BE TRANSPLANTED SUCCESSFULLY IN ANIMAL MODELS OF DISEASES OR INJURIES", "IF STEM CELLS ARE TO BE USED TO TREAT A WIDE VARIETY OF HUMAN DISEASES, THEN WE WILL NEED TO OVERCOME SEVERAL FORMIDABLE CHALLENGES. STEM CELLS WILL BE NEEDED IN LARGE QUANTITIES AND BE ABLE TO DIFFERENTIATED IN A CONTROLLED MANNER TO FORM HOMOGENEOUS POPULATIONS OF CELLS THAT ARE HISTOCOMPATIBLE WITH AN INDIVIDUAL" (left column on page 95). The specification fails to teach whether sufficient quantity of ES cells could be obtained and

propagated *in vitro* for seeding the tissue matrix, and fails to teach whether a relatively pure cell population could be obtained from differentiation of the ES cells so that the prepared tissue matrix could be used as therapeutic means, thus fails to provide an enabling disclosure for the claimed invention.

Moreover, in light of the specification, Claims 22 and 23 appear to be drawn to stimulating said placenta with exogenous cells before collecting ES cells. For example, the specification teaches that the cultured placenta may be stimulated to produce hepatogenic stem cells by introducing exogenous hepatogenic cells or tissue into the placenta (Specification, page 4, lines 20-23). However, since it is well known in the art that the controlled ES cell differentiation is not possible currently, and the specification fails to provide evidence to indicate otherwise, the claimed method does not appear to be enabled in the absence of clarification of the contradictory evidence found in the reference such as *Donovan and Gearhart*. *Pera et al* also teach, "MOST OF THE APPLICATIONS OF HUMAN ES CELLS WILL REQUIRE CELLS TO BE GROWN AND MANIPULATED AS A RELATIVELY PURE STEM CELL POPULATION ON A LARGE SCALE, AND THE AVAILABILITY OF METHODS FOR PRODUCING AND ISOLATING SPECIFIC TYPES OF DIFFERENTIATED CELL FROM THEM. AT PRESENT, NO ONE HAS REPORTED LARGE SCALE GROWTH, EFFICIENT CLONING OR GENETIC MANIPULATION OF HUMAN ES OR EG CELLS", AND "DIRECTED DIFFERENTIATION OF HUMAN ES CELLS INTO SPECIFIC LINEAGES HAS NOT YET BEEN ACHIEVED" (page 9, Conclusion). In view of such, the claimed method does not appear to be enabled.

Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is now claimed.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 11 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Anderson et al* (USP 6,328,762).

Anderson et al teach a tissue matrix (porous prosthetic implant) seeded with cells including embryonic stem cells (e.g. claims 1 and 3), and method of using such for treating a patient to repair or replace tissue (e.g. abstract). Thus, *Anderson et al* anticipate or in the alternative as obvious over the instant claimed invention.

It is noted in this and following rejections, the prior art product differs from the claimed product only by their method of manufacture, i.e. using placenta ES cells or ES

cells from the inner cell mass of blastocyst. However, the claimed method of making the seeded tissue matrix would not distinguish them over the product taught by the prior art. Applicants are reminded that the court has ruled that patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims, and a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985).

Claims 11 and 12 are rejected under 35 U.S.C. 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Wu et al* (US 2003/0109042).

Wu et al teach a tissue matrix comprising a three dimensional support for stem cells including embryonic stem cells (e.g. claims 1 and 5), wherein the 3-D scaffolding is made of different porous or fibrous materials including natural polymers (paragraph 0078), and method of using such for treating a patient to repair or replace tissue (paragraph 0124). Thus, *Wu et al* anticipate or in the alternative as obvious over the instant claimed invention.

Claims 11 and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over *Buttery et al* (Tissue Eng 2001;7:89-99).

Buttery et al teach a tissue matrix comprising an embryonic feeder cell layer seeded with mouse embryonic stem cells (last paragraph, page 90), and another tissue matrix comprising fetal osteoblasts, collagens seeded with ES cells (2nd section, page 91), and method of using such for treating a patient to repair or replace tissue (e.g. last paragraph, page 97). Thus, *Buttery et al* anticipate or in the alternative as obvious over the instant claimed invention.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance.

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Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



Q. Janice Li
Primary Examiner
Art Unit 1632

GJL
September 17, 2004